

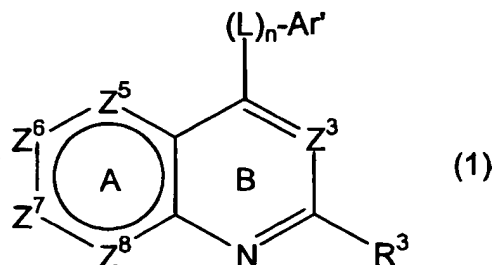
Application No.: 09/972,582

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**In the Claims**

1. (Currently Amended): A method to inhibit p38 $\alpha$  activity, which method comprises contacting said p38 $\alpha$  with a compound of the formula:



or the pharmaceutically acceptable salts thereof

wherein R<sup>3</sup> comprises a substituted or unsubstituted aromatic moiety, wherein said aromatic moiety is a monocyclic or fused bicyclic moiety containing 5-12 ring member atoms, optionally comprising one or more heteroatoms selected from O, S and N;

wherein Z<sup>3</sup> is N, Z<sup>5</sup> is CH, and Z<sup>6</sup> and Z<sup>7</sup> are CR<sup>2</sup> and each remaining Z is CR<sup>2</sup> or N, wherein no more than two Z positions in ring A are N, and wherein two adjacent Z positions in ring A cannot be N;

Z<sup>8</sup> is CH or N;

each R<sup>2</sup> is either

(i) independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyl, wherein each of alkyl, alkenyl, alkynyl and acyl may optionally contain 1-2 O, S or N, aryl, and arylalkyl, each of said aryl and arylalkyl optionally containing 1 or more O, S or N and wherein in each of the foregoing other than H may be unsubstituted or substituted with 1-3 substituents selected independently from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR<sub>2</sub>, SR, -SOR, -SO<sub>2</sub>R, -OCOR, -NRCOR, -NRCONR<sub>2</sub>, -NRCOOR, -NRSOR, -NRSO<sub>2</sub>R, -OCONR<sub>2</sub>, RCO, -COOR, -SO<sub>3</sub>R, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or alkyl (1-4C), and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR<sub>2</sub>, SR, -SOR, -SO<sub>2</sub>R, -OCOR, -NRCOR, -NRCONR<sub>2</sub>, -NRCOOR, -NRSOR, -NRSO<sub>2</sub>R, -OCONR<sub>2</sub>, RCO, -COOR, -SO<sub>3</sub>R, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or alkyl (1-4C), or

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(ii) independently selected from the group consisting of halo, OR, NR<sub>2</sub>, SR, -SOR, -SO<sub>2</sub>R, -OCOR, -NRCOR, -NRCONR<sub>2</sub>, -NRCOOR, NRSOR, NRSO<sub>2</sub>R, -OCONR<sub>2</sub>, RCO, -COOR, -SO<sub>3</sub>R, NRSOR, NRSO<sub>2</sub>R, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or alkyl (1-4C);

wherein L is R<sup>1</sup>N(CH<sub>2</sub>)<sub>n</sub> wherein R<sup>1</sup> is H, alkyl (1-6C) or arylalkyl optionally substituted on the aryl moiety with 1-3 substituents independently selected from the group consisting of alkyl (1-6C), halo, OR, NR<sub>2</sub>, SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or alkyl (1-4C); ~~a divalent moiety that provides a distance of 2-8Å between ring B and Ar'~~;

n is 0 or 1; and

(a) Ar' is phenyl, substituted with at least one group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR<sub>2</sub>, SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or lower alkyl (1-4C), or pyridyl, indolyl, or pyrimidyl, each optionally substituted with at least one group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR<sub>2</sub>, SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or lower alkyl (1-4C); and

R<sup>3</sup> is phenyl optionally substituted with 1-3 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, OR, NR<sub>2</sub>, SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, -SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or lower alkyl (1-4C); or

(b) Ar' is phenyl, pyridyl, indolyl, or pyrimidyl, each optionally substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR<sub>2</sub>, SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or lower alkyl (1-4C); and

R<sup>3</sup> is phenyl substituted with 1-3 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, -SO<sub>2</sub>NR<sub>2</sub>, CN, and CF<sub>3</sub>, wherein each R is independently H or lower alkyl (1-4C); or

(c) Ar' is phenyl substituted with a group selected from the group consisting of optionally substituted NR<sub>2</sub>, SR, -NROCR, RCO, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, and CF<sub>3</sub>, wherein each R is independently H or lower alkyl (1-4C); or pyridyl substituted with a group selected from the group

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consisting of optionally substituted alkyl (1-6C), halo, OR, NR<sub>2</sub>, SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or lower alkyl (1-4C); or indolyl or pyrimidyl, each optionally substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR<sub>2</sub>, SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or lower alkyl (1-4C); and

R<sup>3</sup> is phenyl optionally substituted with 1-3 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, OR, NR<sub>2</sub>, SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, -SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or lower alkyl (1-4C); or

(d) Ar' is phenyl, pyridyl, indolyl, or pyrimidyl, each optionally substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR, NR<sub>2</sub>, SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or lower alkyl (1-4C); and

R<sup>3</sup> is phenyl substituted with 1-3 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, OR, SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, -SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or lower alkyl (1-4C).

~~Ar' is a cyclic hydrocarbyl aliphatic, cyclic hydrocarbyl aliphatic containing one or more heteroatoms or a monocyclic or polycyclic aromatic moiety any of the foregoing optionally substituted with 1-3 substituents, wherein two of said substituents may form a 5-7 member cyclic optionally heterocyclic aliphatic ring and wherein Ar' and any said substituents thereon forming a cyclic aliphatic ring, may optionally contain one or more ring atoms selected from O, S and N, wherein said compound inhibits p38 $\alpha$  activity.~~

2-7. (canceled)

8. (previously presented): The method of claim 1 wherein any substituents on the aromatic or heteroaromatic moiety of R<sup>3</sup> are independently selected from the group consisting of halo, OR, NR<sub>2</sub>, SR, -SOR, -SO<sub>2</sub>R, -OCOR, -NRCOR, -NRCONR<sub>2</sub>, -NRCOOR, -NRSOR,

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-NRSO<sub>2</sub>R, -OCONR<sub>2</sub>, RCO, -COOR, -SO<sub>3</sub>R, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or alkyl (1-4C) and alkyl (1-6C).

9. (original): The method of claim 1 wherein said substituents on substituted Ar' are independently selected from the group consisting of optionally substituted alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR<sub>2</sub>, SR, -SOR, -SO<sub>2</sub>R, -OCOR, -NRCOR, -NRCONR<sub>2</sub>, -NRCOOR, -NRSOR, -NRSO<sub>2</sub>R, -OCONR<sub>2</sub>, RCO, -COOR, -SO<sub>3</sub>R, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or alkyl (1-4C), and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR<sub>2</sub>, SR, -SOR, -SO<sub>2</sub>R, -OCOR, -NRCOR, -NRCONR<sub>2</sub>, -NRCOOR, -NRSOR, -NRSO<sub>2</sub>R, -OCONR<sub>2</sub>, RCO, -COOR, -SO<sub>3</sub>R, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or alkyl (1-4C).

10. (previously presented): The method of claim 9 wherein Ar' is phenyl, 2-, 3-, or 4-pyridyl, 2- or 4-pyrimidyl, indolyl, isoquinolyl, quinolyl, benzimidazolyl, benzotriazolyl, benzothiazolyl, benzofuranyl, pyridyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, or imidazolyl, all of which may optionally be substituted.

11-12. (canceled)

13. (previously amended): The method of claim 1 wherein said optional substituents on R<sup>2</sup> are independently selected from the group consisting of R<sup>4</sup>, halo, OR<sup>4</sup>, NR<sup>4</sup><sub>2</sub>, SR<sup>4</sup>, -OOCR<sup>4</sup>, -NROCR<sup>4</sup>, -COOR<sup>4</sup>, R<sup>4</sup>CO, -CONR<sup>4</sup><sub>2</sub>, -SO<sub>2</sub>NR<sup>4</sup><sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R<sup>4</sup> is independently H, or optionally substituted alkyl (1-6C), or optionally substituted arylalkyl (7-12C) and wherein two R<sup>4</sup> or two substituents on said alkyl or arylalkyl taken together may form a fused aliphatic ring of 5-7 members.

14-15. (canceled)

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16. (currently amended): The method of claim 1 wherein the compound of formula (1) is selected from group consisting of

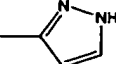
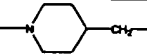
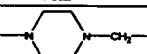
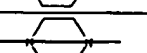
(a) the compounds listed in Table 2 below, wherein ~~Z<sup>5</sup>-Z<sup>8</sup> are CH~~; Z<sup>3</sup> is N; R<sup>1</sup> in compound No. 11 is 2-propyl; R<sup>1</sup> in compound No. 12 is 4-methoxyphenyl, and R<sup>1</sup> in compound No. 41 is 4-methoxybenzyl; and wherein L, Ar' and R<sup>3</sup> are as shown in Table 2:

Table 2			
Compound No.	L	Ar'	R <sup>3</sup>
1	NH	4-pyridyl	2-chlorophenyl
2	NH	4-pyridyl	2,6-dichlorophenyl
3	NH	4-pyridyl	2-methylphenyl
4	NH	4-pyridyl	2-bromophenyl
5	NH	4-pyridyl	2-fluorophenyl
6	NH	4-pyridyl	2,6-difluorophenyl
7	NH	4-pyridyl	phenyl
8	NH	4-pyridyl	4-fluorophenyl
9	NH	4-pyridyl	4-methoxyphenyl
10	NH	4-pyridyl	3-fluorophenyl
11	NR <sup>1</sup>	4-pyridyl	phenyl
12	NR <sup>1</sup>	4-pyridyl	phenyl
13	NHCH <sub>2</sub>	4-pyridyl	phenyl
14	NHCH <sub>2</sub>	4-pyridyl	4-chlorophenyl
15	NH	3-pyridyl	phenyl
16	NHCH <sub>2</sub>	2-pyridyl	phenyl
17	NHCH <sub>2</sub>	3-pyridyl	phenyl
18	NHCH <sub>2</sub>	2-pyridyl	phenyl
19	NHCH <sub>2</sub> CH <sub>2</sub>	2-pyridyl	phenyl
20	NH	6-pyrimidinyl	phenyl
21	NH	2-pyrimidinyl	phenyl
22	NH	Phenyl	phenyl
23	NHCH <sub>2</sub>	Phenyl	3-chlorophenyl
24	NH	3-hydroxyphenyl	phenyl
25	NH	2-hydroxyphenyl	phenyl
26	NH	4-hydroxyphenyl	phenyl
27	NH	4-indolyl	phenyl
28	NH	5-indolyl	phenyl
29	NH	4-methoxyphenyl	phenyl

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Table 2			
Compound No.	L	Ar'	R <sup>3</sup>
30	NH	3-methoxyphenyl	phenyl
31	NH	2-methoxyphenyl	phenyl
32	NH	4-(2-hydroxyethyl)phenyl	phenyl
33	NH	3-cyanophenyl	phenyl
34	NHCH <sub>2</sub>	2,5-difluorophenyl	phenyl
35	NH	4-(2-butyl)phenyl	phenyl
36	NHCH <sub>2</sub>	4-dimethylaminophenyl	phenyl
38	NH	2-pyridyl	phenyl
39	NHCH <sub>2</sub>	3-pyridyl	phenyl
40	NH	4-pyrimidyl	phenyl
41	NR <sup>1</sup>	4-pyridyl	phenyl
42	NH	p-aminomethylphenyl	phenyl
43	NHCH <sub>2</sub>	4-aminophenyl	phenyl
44	NH	4-pyridyl	3-chlorophenyl
45	NH	Phenyl	4-pyridyl
46	NH		phenyl
48	NH	2-benzylamino-3-pyridyl	phenyl
49	NH	2-benzylamino-4-pyridyl	phenyl
50	NH	3-benzyloxyphenyl	phenyl
51	NH	4-pyridyl	3-aminophenyl
52	NH	4-pyridyl	4-pyridyl
53	NH	4-pyridyl	2-naphthyl
54		4-pyridyl	phenyl
55		Phenyl	phenyl
56		2-pyridyl	phenyl
61	NH	4-pyridyl	2-trifluoromethyl phenyl
62	NH	4-aminophenyl	phenyl
64	NH	3-methoxyphenyl	2-fluorophenyl
65	NH	4-methoxyphenyl	2-fluorophenyl
66	NH	4-pyrimidinyl	2-fluorophenyl

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Table 2			
Compound No.	L	Ar'	R <sup>3</sup>
67	NH	3-amino-4-pyridyl	phenyl
68	NH	4-pyridyl	2-benzylaminophenyl
69	NH	2-benzylaminophenyl	phenyl
70	NH	2-benzylaminophenyl	4-cyanophenyl
71	NH	3'-cyano-2-benzylaminophenyl	phenyl

(b) the compounds listed in Table 3, below, wherein L is NH; Z<sup>3</sup> is N; Z<sup>6</sup> and Z<sup>7</sup> are CH and Z<sup>5</sup>, Z<sup>8</sup>, Ar' and R<sup>3</sup> are as shown in Table 3:

Table 3				
Compound No.	Z <sup>5</sup>	Z <sup>8</sup>	Ar'	R <sup>3</sup>
72	CH	N	4-pyridyl	2-fluorophenyl
73	CH	N	4-pyridyl	2-chlorophenyl
74	CH	N	4-pyridyl	phenyl
75	N	N	4-pyridyl	phenyl
76	N	CH	4-pyridyl	phenyl

and

(c) the quinazoline derivatives listed in Table 4 below, wherein L is NH; Ar' is 4-pyridyl; Z<sup>3</sup>, [[Z<sup>5</sup>,]] and Z<sup>8</sup> are N; Z<sup>5</sup> is CH, Z<sup>6</sup> or Z<sup>7</sup> are CR<sup>2</sup> as shown and each is otherwise N and wherein R<sup>3</sup> and R<sup>2</sup> are as shown in Table 4:

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Table 4		
Compound No.	R <sup>3</sup>	R <sup>2</sup>
77	2-chlorophenyl	6,7-dimethoxy
78	2-fluorophenyl	6-nitro
79	2-fluorophenyl	6-amino
80	2-fluorophenyl	7-amino
81	2-fluorophenyl	6-(3-methoxybenzylamino)
82	2-fluorophenyl	6-(4-methoxybenzylamino)
83	2-fluorophenyl	6-(2-isobutylamino)
84	2-fluorophenyl	6-(4-methylmercaptobenzylamino)
85	2-fluorophenyl	6-(4-methoxybenzoyl amino)
86	4-fluorophenyl	7-amino
87	4-fluorophenyl	7-(3-methoxybenzylamino)

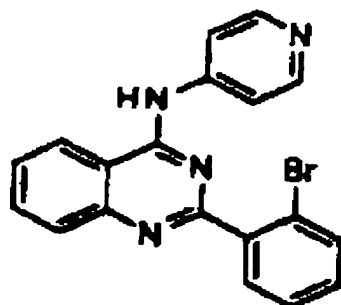
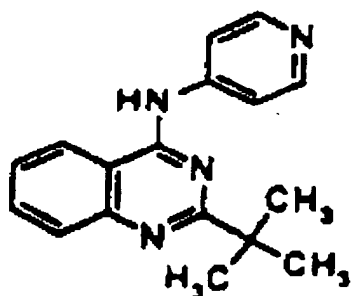
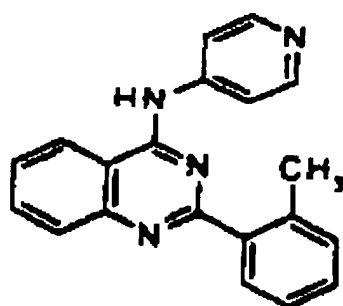
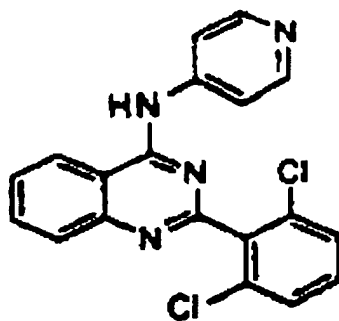
17. (previously presented): The method of claim 1 wherein the compound of formula (1) is selected from the group consisting of the following compounds:



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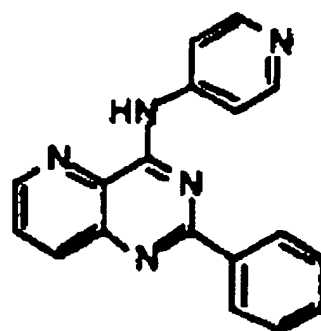
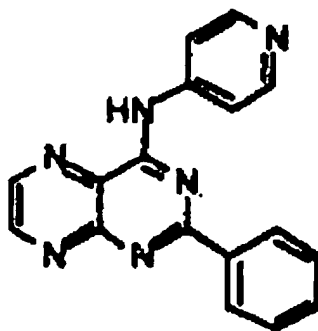
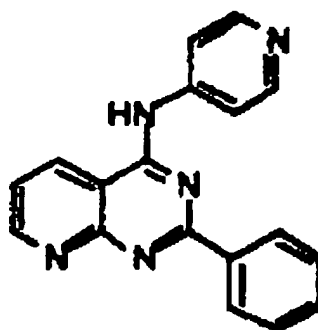
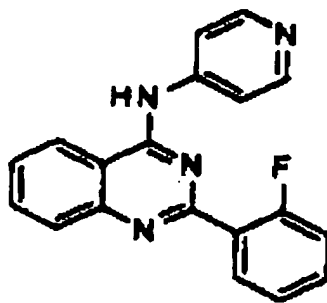
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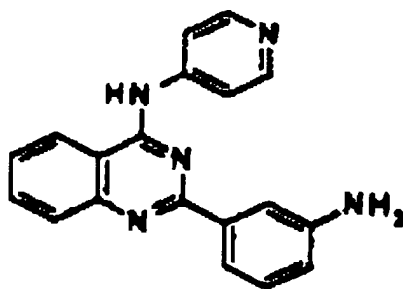
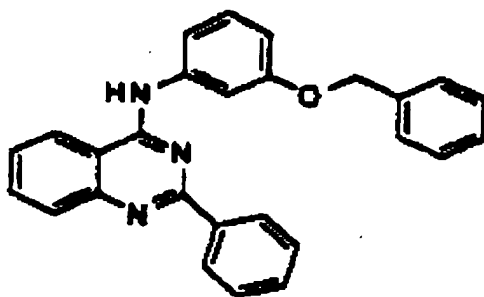
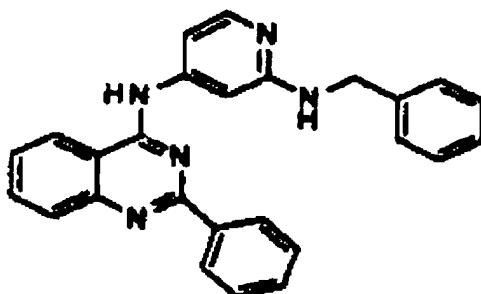
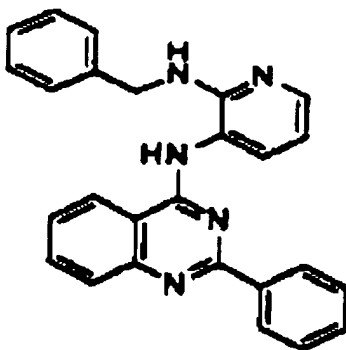


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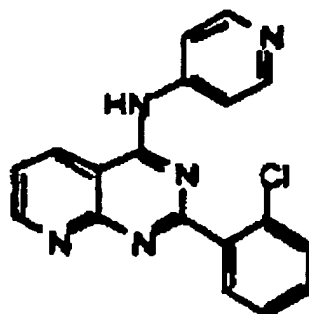
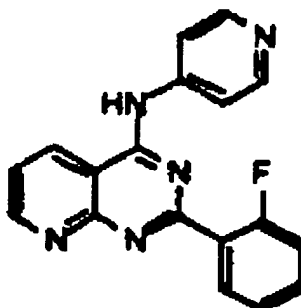
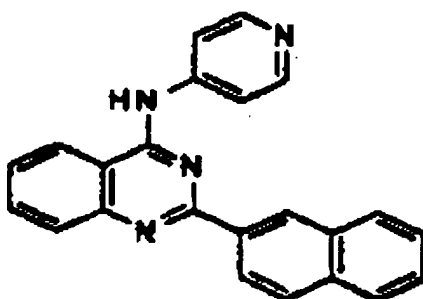
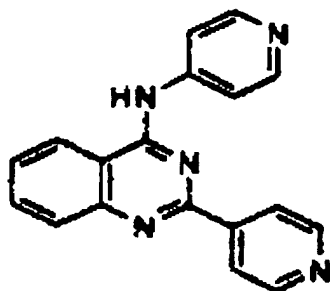


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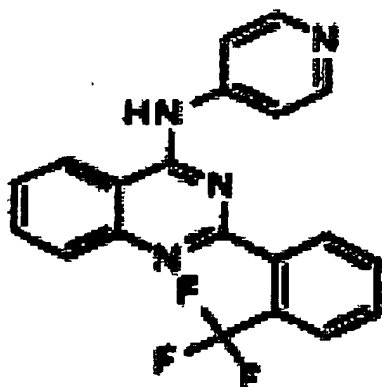
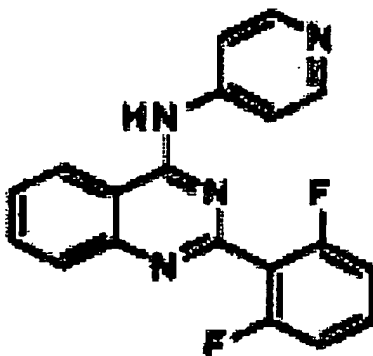
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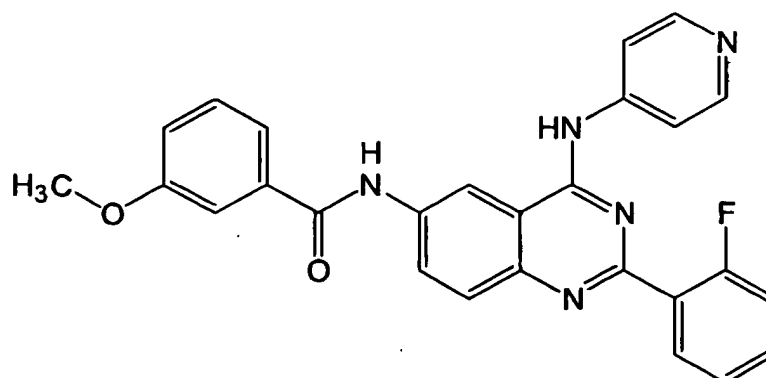
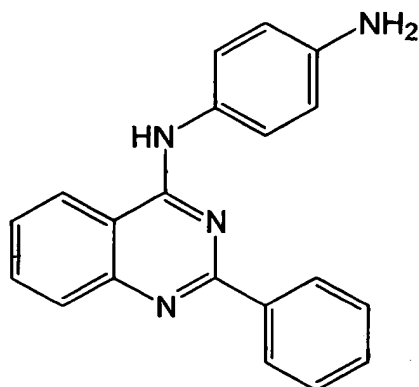
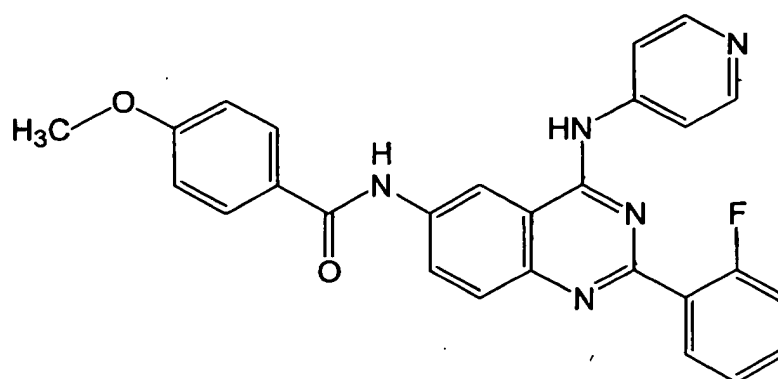
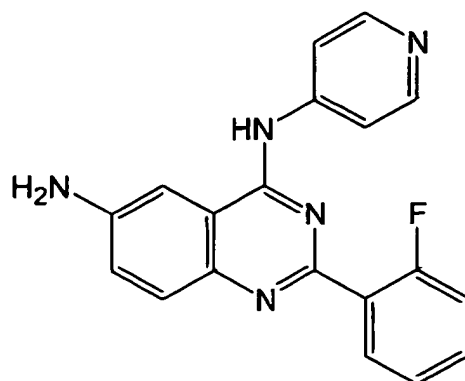


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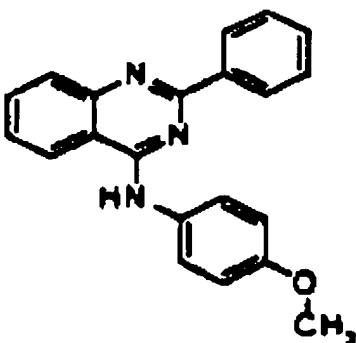
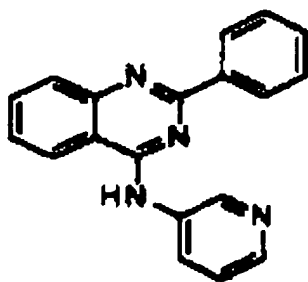
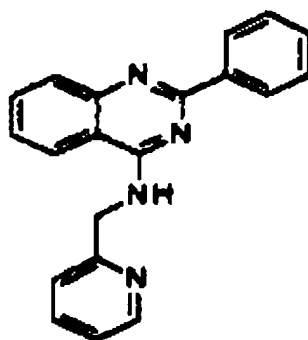
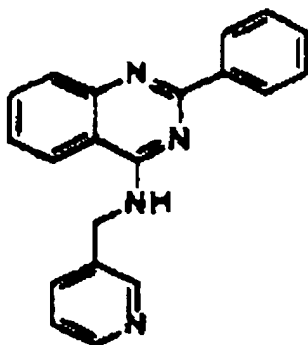
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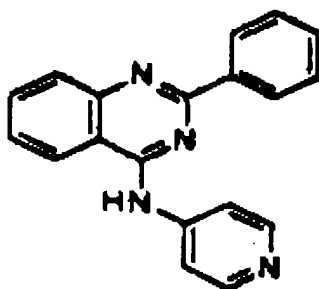
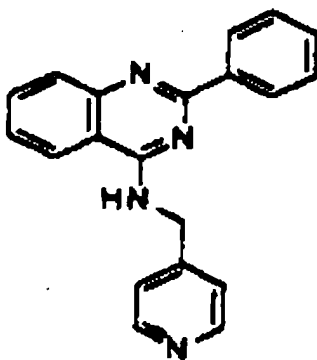
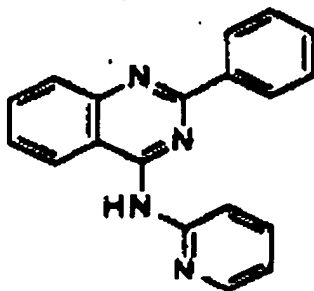


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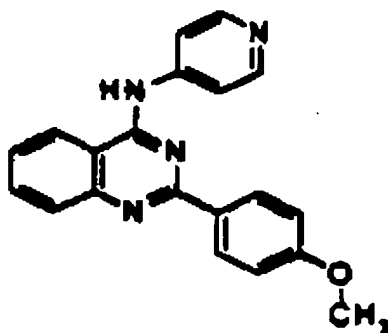
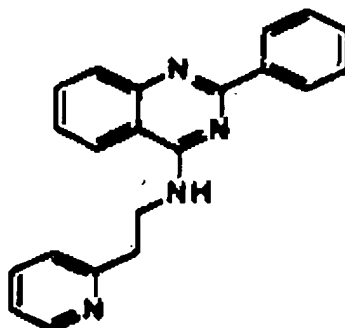
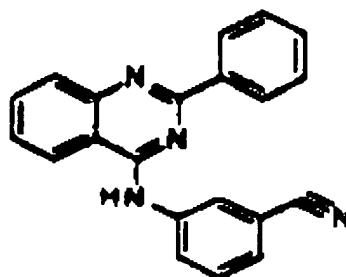
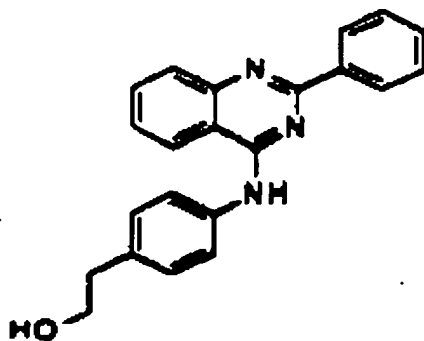




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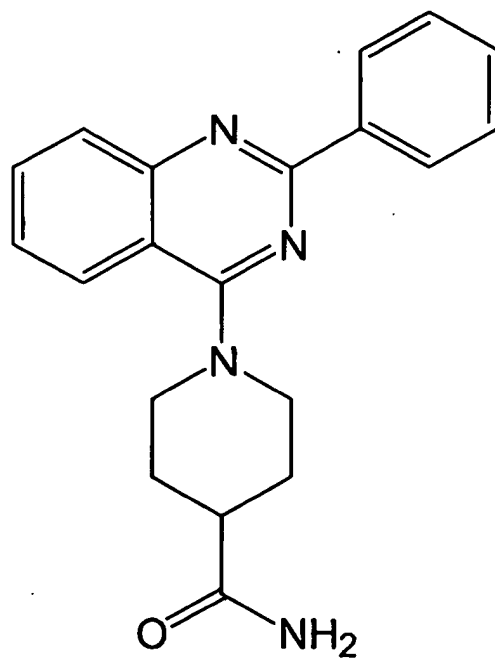
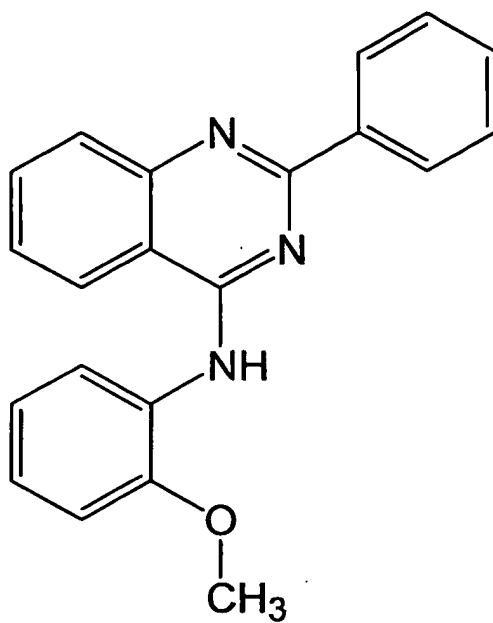


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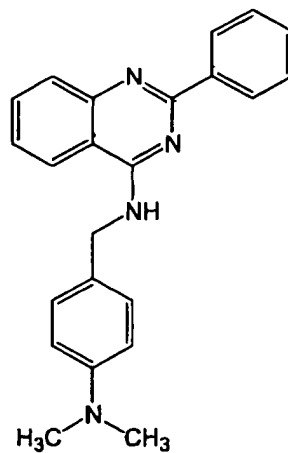
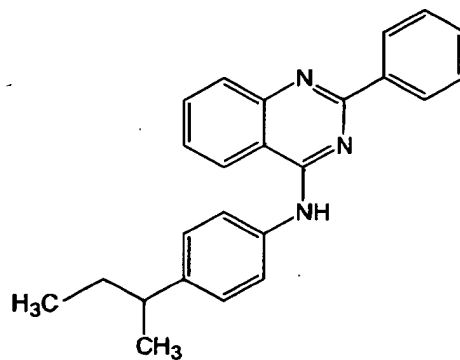
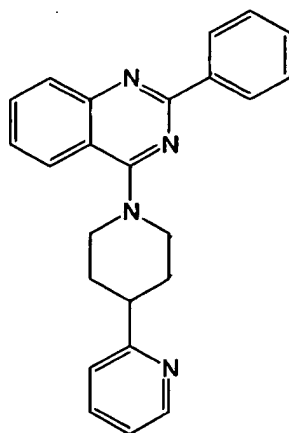
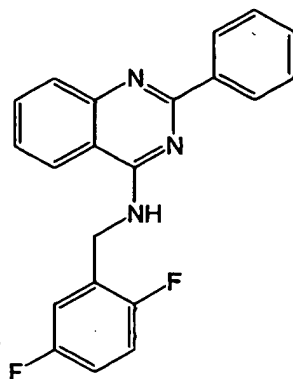


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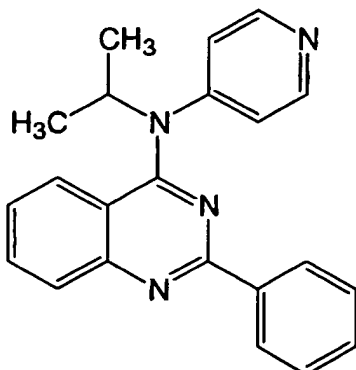
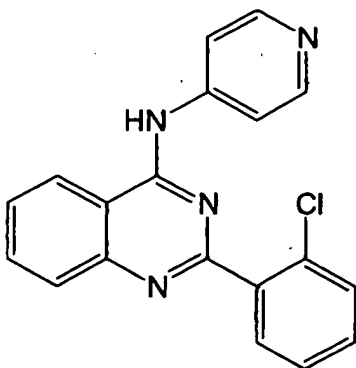
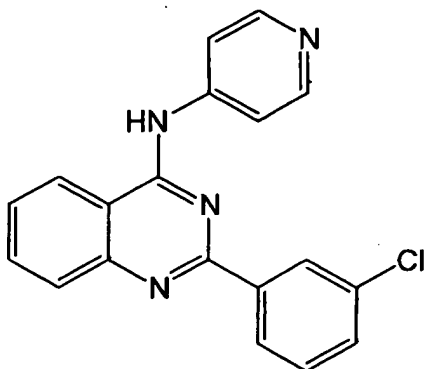
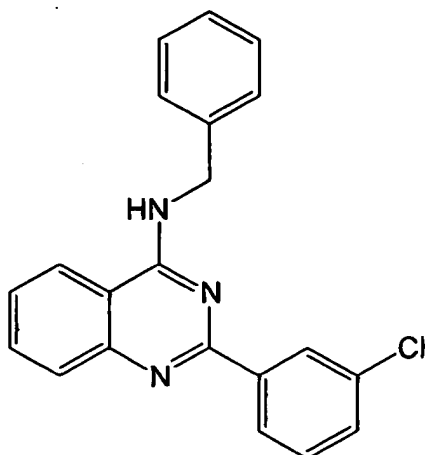


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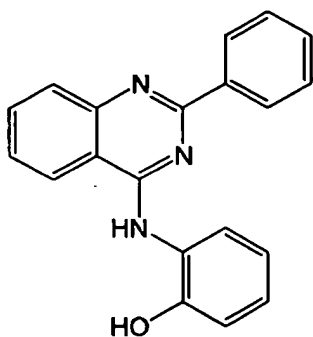
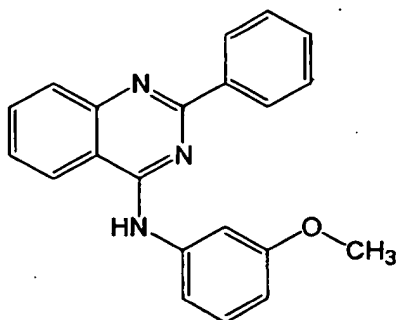
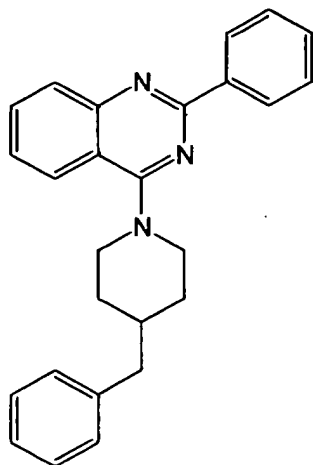
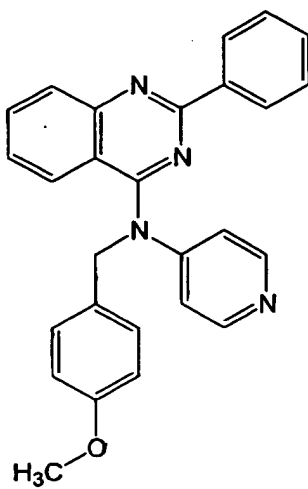
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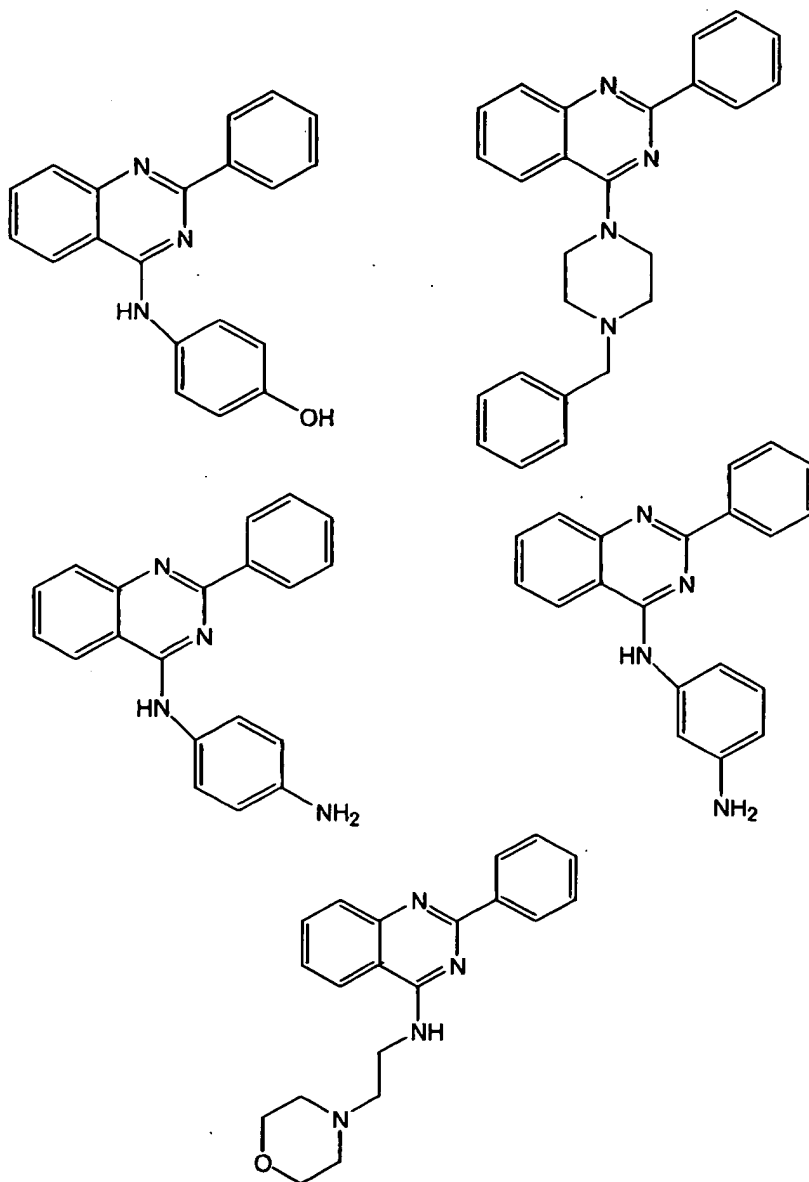


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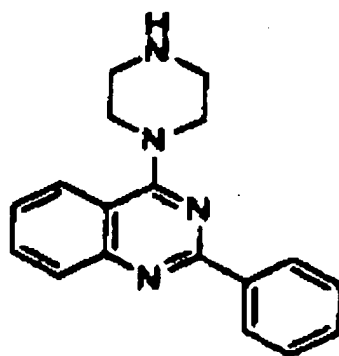
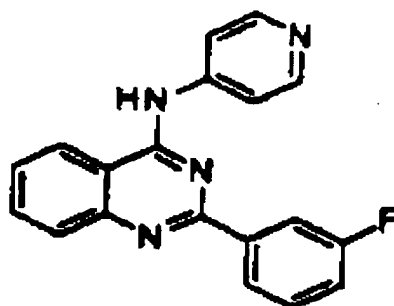
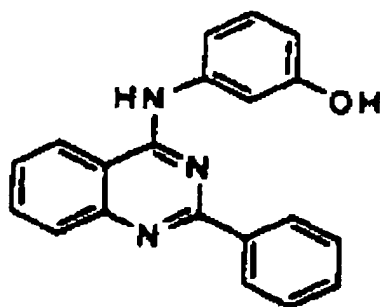


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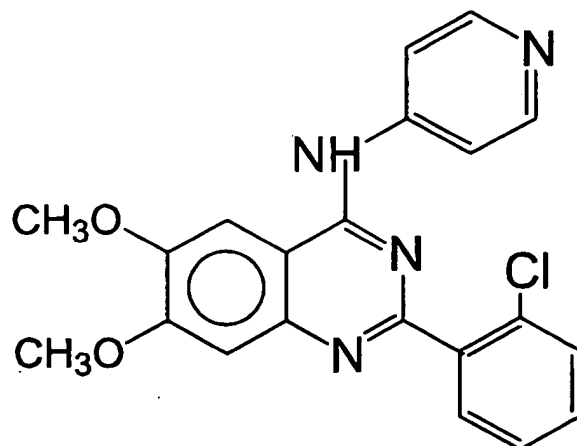
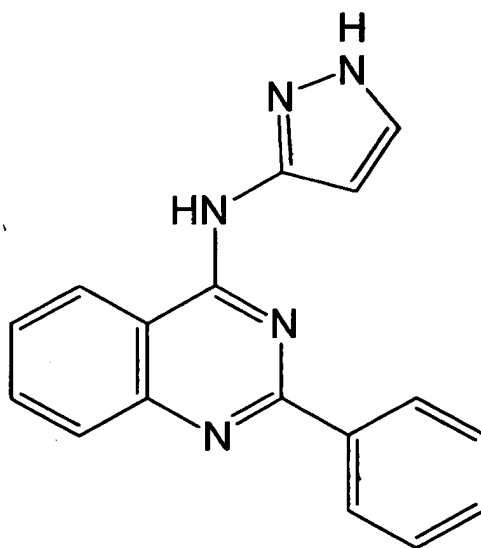
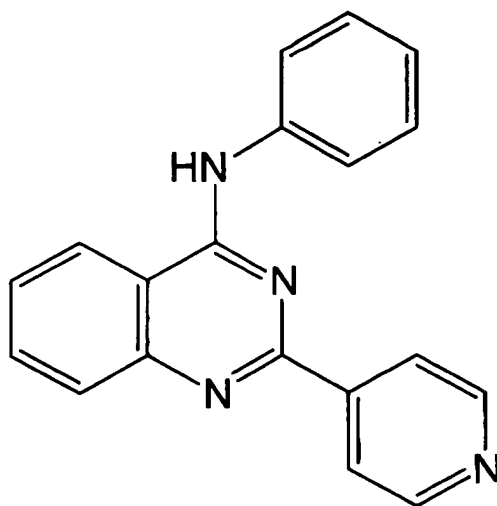


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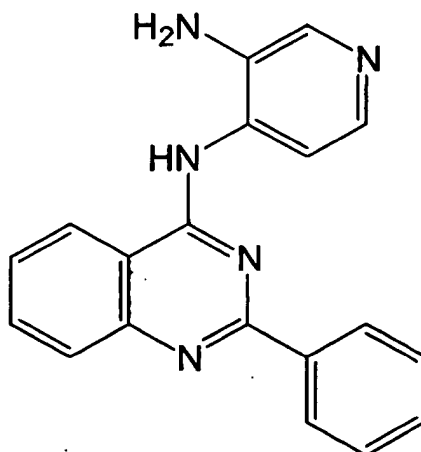
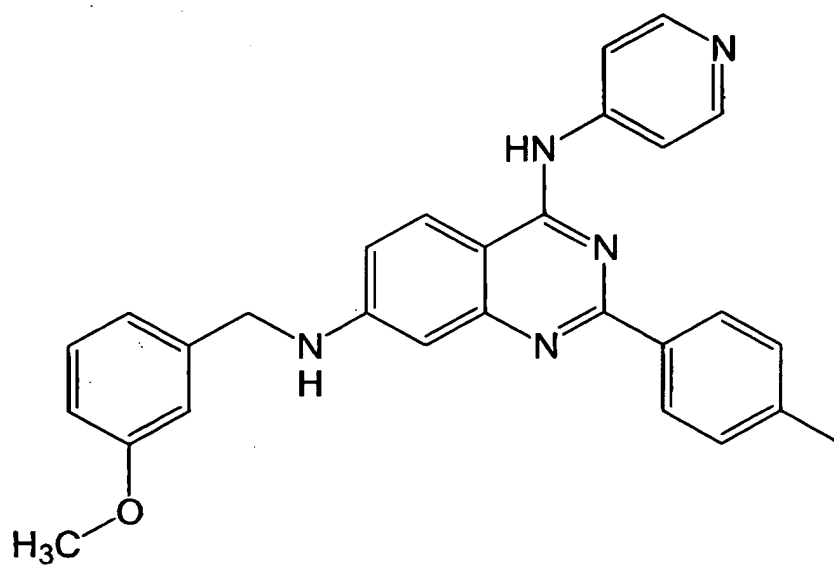
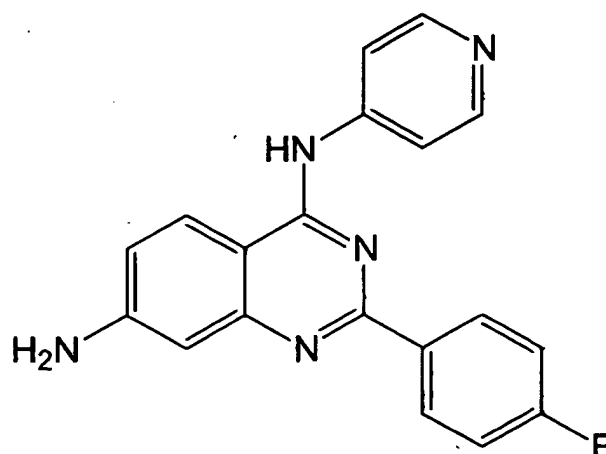




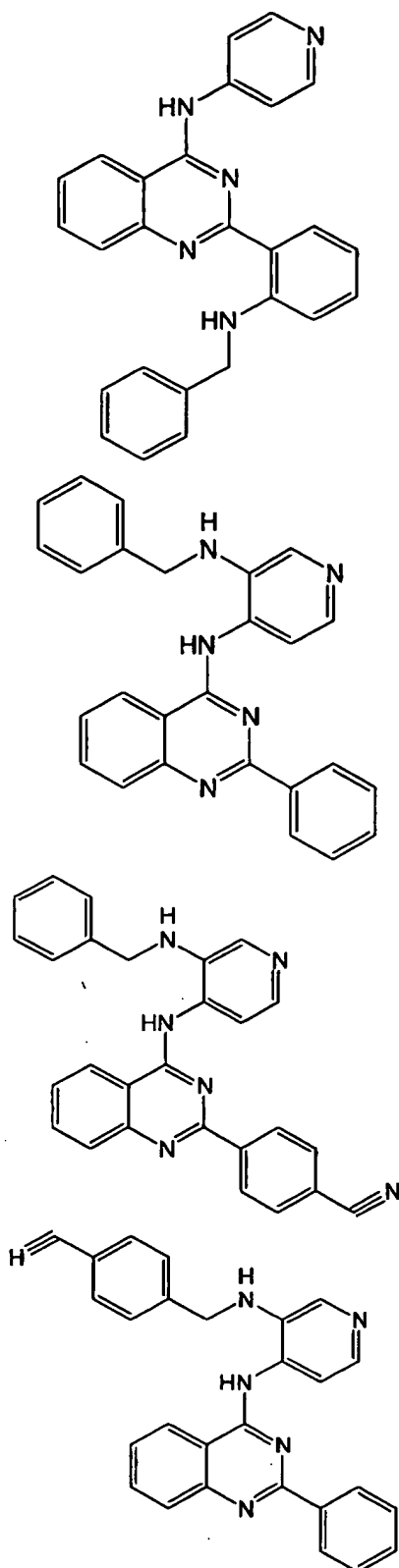
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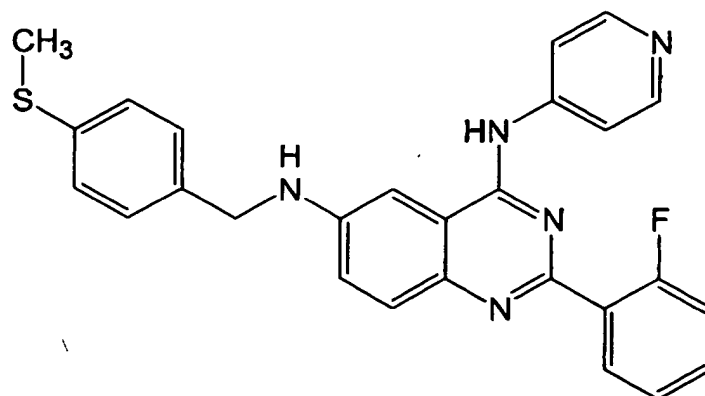
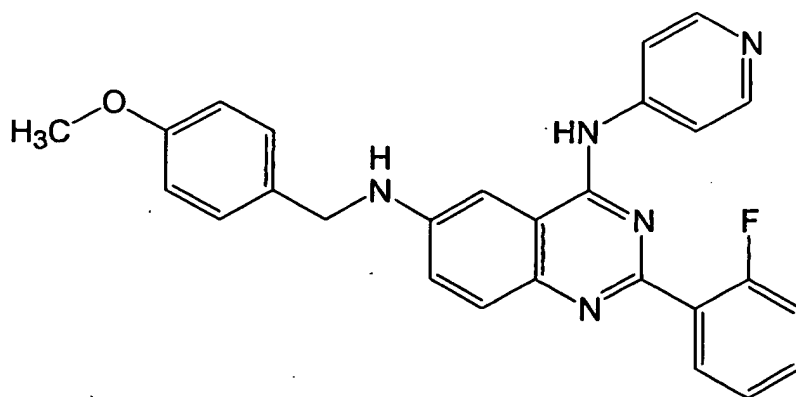
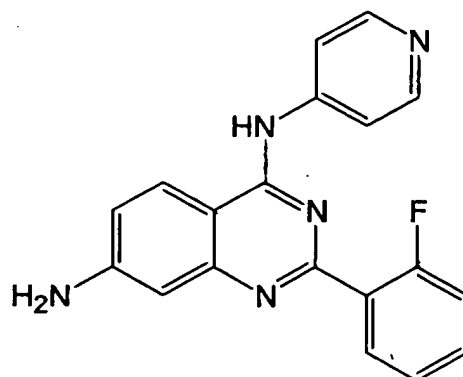
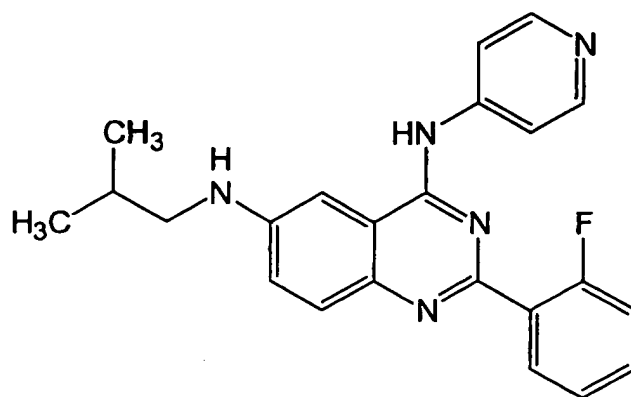


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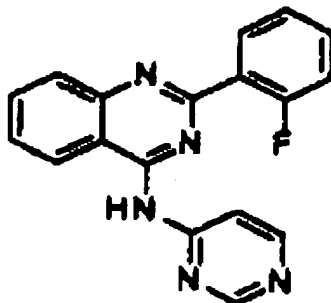
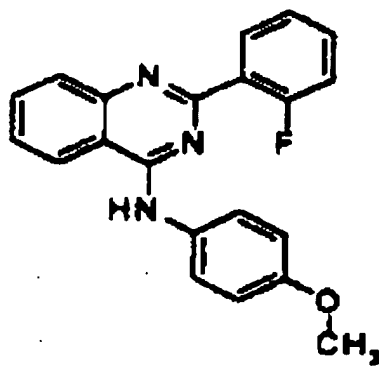
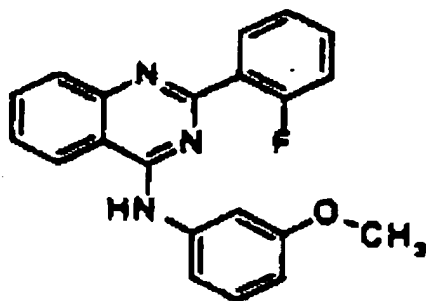
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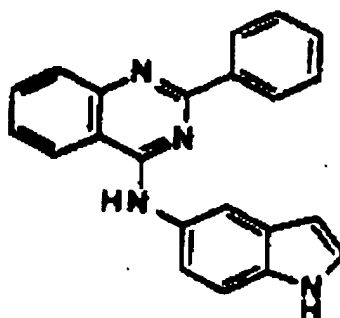
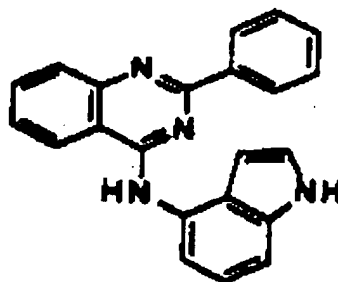
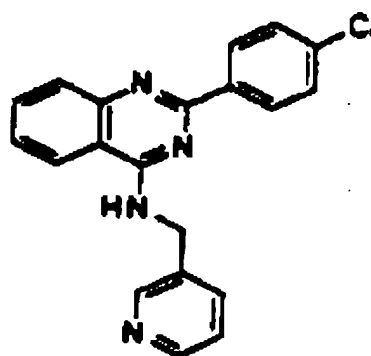
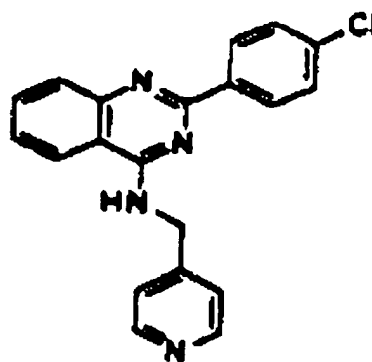


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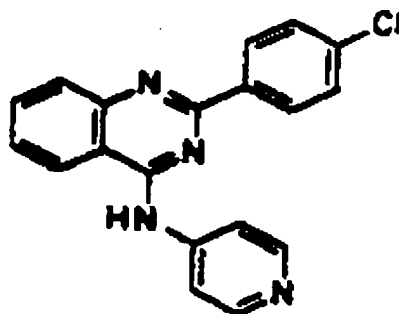
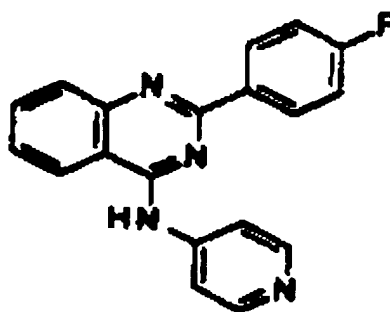
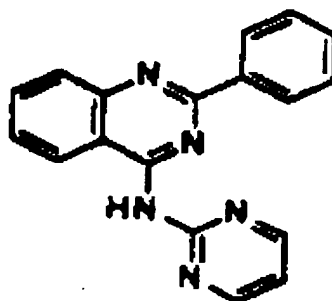
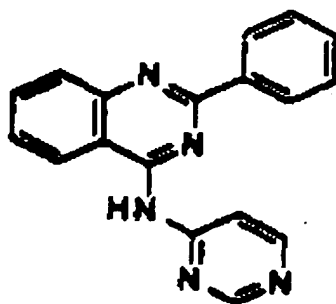


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18-23. (canceled)

24. (previously presented): The method of claim 1 wherein the compound of formula 1 is selected from the group consisting of

2-phenyl-4-(4-pyridylamino)-quinazoline;  
2-(2-bromophenyl)-4-(4-pyridylamino)-quinazoline;  
2-(2-chlorophenyl)-4-(4-pyridylamino)-quinazoline;  
2-(2-fluorophenyl)-4-(4-pyridylamino)-quinazoline;  
2-(2-methylphenyl)-4-(4-pyridylamino)-quinazoline;  
2-(4-fluorophenyl)-4-(4-pyridylamino)-quinazoline;  
2-(3-methoxyanilyl)-4-(4-pyridylamino)-quinazoline;  
2-(2,6-dichlorophenyl)-4-(4-pyridylamino)-quinazoline;  
2-(2,6-dibromophenyl)-4-(4-pyridylamino)-quinazoline;  
2-(2,6-difluorophenyl)-4-(4-pyridylamino)-quinazoline;  
2-(2-fluorophenyl)-4-(4-pyridylamino)-6, 7-dimethoxyquinazoline;  
2-(4-fluorophenyl)-4-(4-pyridylamino)-6, 7-dimethoxyquinazoline;  
2-(2-fluorophenyl)-4-(4-pyridylamino)-6-nitroquinazoline;  
2-(2-fluorophenyl)-4-(4-pyridylamino)-6-aminoquinazoline;  
2-(2-fluorophenyl)-4-(4-pyridylamino)-7-aminoquinazoline;  
2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(3-methoxybenzylamino)-quinazoline;  
2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(4-methoxybenzylamino)-quinazoline;  
2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(2-isobutylamino)-quinazoline; and  
2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(4-methylmercaptobenzylamino)-quinazoline.

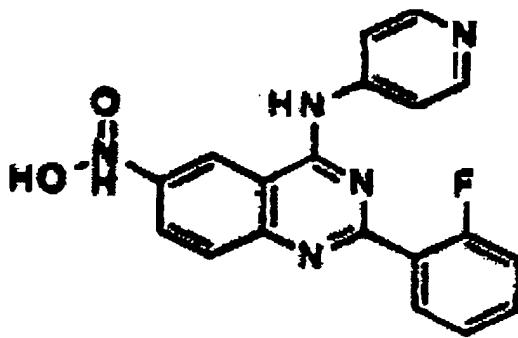
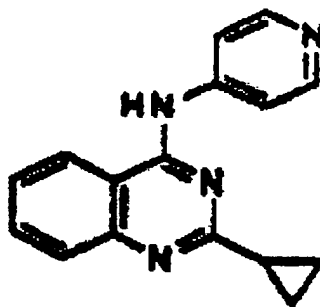
25-33. (canceled)

34. (previously presented): A method to inhibit p38 $\alpha$  activity, which method comprises contacting said p38 $\alpha$  with a compound selected from the group consisting of

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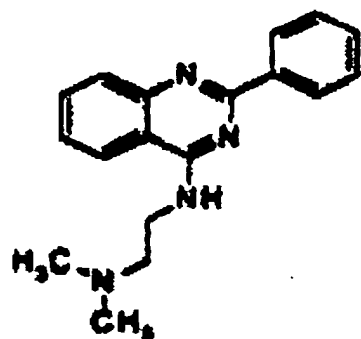




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, and

